TERRAMYCIN IN EARLY LYMPHOGRANULOMA VENEREUM*

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In May and June, 1951, at the British Military Hospital, Accra, and between September, 1951, and February, 1952, at the Military Hospital, Kaduna, patients suffering from lymphogranuloma venereum, uncomplicated by disease other than venereal, were treated with terramycin.

Material

Altogether nineteen cases were treated, six at Accra, thirteen at Kaduna. All were adult male Africans, members of the Royal West African Frontier Force, between the ages of 20 and 30.

Cases were seen early, the mean duration of symptoms before admission being approximately 8 days. No reliable information as to exposure was obtainable. Clinical examination and a Kahn reaction were carried out in all cases. No Frei antigen was available at Accra, where the diagnosis was made on clinical grounds, but all cases at Kaduna gave a positive skin reaction to antigen prepared by Frei's original method (Frei, 1925).

Method

All investigations having been completed, the patients were divided into four groups, according to the severity of the lesions :

Group 1—Inguinal adenitis without fixation of skin.
Group 2—Inguinal adenitis with fixation of skin but without fluctuation or suppuration.
Group 3—Inguinal adenitis with fluctuation, but without open suppuration.
Group 4—Inguinal adenitis with open suppuration, sinus formation etc.

No case showed ano-rectal involvement.

In Group 3, in addition to antibiotic therapy, aspiration of buboes was carried out whenever a moderate quantity of pus had collected. Patients were only aspirated before treatment commenced if the skin threatened to break down. In cases of Group 4, magnesium sulphate dressings were repeated as often as necessary. No other local treatment was given.

All patients received 1 g. terramycin 6-hourly for the duration of treatment. Progress in terms of the severity of the lesions as defined by the above groups was assessed daily. Cure was said to have been achieved when, in the words of Alergant (1950), " the inguinal glands were firm, discrete, and no longer tender ", although some enlargement may have remained.

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Results

Eighteen cases were cured, but one patient—with a positive Frei test and a positive Kahn reaction—had deteriorated from Group 2 to Group 3 after 11 days (44 mg.) and was regarded as a therapeutic failure. Patients have been followed for a period of between 1 and 8 months, and none has relapsed. The progress of the eighteen cured cases is shown in Table I.

TABLE I

ANALYSIS OF 18 CASES CURED BY TERRAMYCIN

Initial Group	Number of Cases	Mean Duration of Treatment (days)	
		To first improvement *	To cure
1	5	—	4
2	7	4·3	7·3
3	3	4·3	9·3
4	3	4·3	9·3
	Mean	4·3	7·0

* " First improvement " indicates the time taken for cases of groups 2–4 to be permanently assigned to a lower group.
S.D. of mean duration of treatment to cure = 2·97.

It therefore appears that noticeable improvement is usually seen within 4 days, and that cure was achieved within an average of just over a week (i.e. after 28 g. of the drug had been taken). A positive Kahn reaction did not appear to increase the time taken to achieve cure.

In view of the possibilities of false positive reactions due to malaria, old yaws, or other endemic diseases, a Kahn titre of " 3 " or more in at least one of the tubes was considered necessary for a diagnosis of latent syphilis.

Toxic Manifestations.—These were minimal or absent in eighteen cases and mild in one. There was never any question of discontinuing treatment, in spite of the comparatively large doses given. The symptoms found were as follows :

diarrhoea and loose stools (2) ; brown coated tongue (6) ; headache (1) ; change of taste (1) ; rectal irritation (1).

In addition, some patients exhibited febrile reactions, up to a temperature of 101° F., but in an area where short-term fevers of malarial and non-malarial origin are common, such incidents are not necessarily attributable to the drug used.

Comparison of Treatments.—To enable comparisons with the standard treatment previously in use to be made, the case records were examined of patients diagnosed as suffering from lymphogranuloma venereum, and admitted to the Military Hospital, Kaduna, between August 1, 1950, and September 1, 1951. During the two periods of observation the exposed population with access to in-patient treatment in the military hospital remained substantially the same in composition and numbers. Although it is not possible, in retrospect, to subdivide these cases into Groups 1-4, there is no evidence of any factors which would alter the distribution of the two series of cases among those groups. Patients whose records were incomplete or left some doubt as to correctness of diagnosis, or as to actual duration of treatment, were excluded. Less than five were found to relapse within a month. These were regarded as true relapses and periods of treatment on both admissions were combined and regarded as a single admission. Relapses after one month were considered to be re-infections, and constituted two separate cases. These patients received 6 g. of an available sulphonamide drug daily for a variable number of days (the course being lengthened, shortened, or repeated as necessary), and also 2 ml. lithium antimony thiomalate on alternate days up to a maximum of 10 ml., this also being increased and reduced as necessary. Results compared with those obtained by the use of terramycin are given in Table II.

TABLE II
STANDARD TREATMENT COMPARED WITH TERRAMYCIN (CURED CASES ONLY)

Type of Treatment	Standard (all groups)	Terramycin (all groups)
Number of Cases	46	18
Mean Duration of Treatment (days)	13·65	7·015
Standard Deviation	6·465	2·973

Difference of mean (standard and terramycin) 6·635
Standard error of difference 1·2
The difference is, therefore, highly significant.

Discussion

Before the advent of the newer antibiotics, lymphogranuloma venereum was treated by sulphonamides, especially sulphamerazine (Rake, 1948). These were occasionally reinforced by compounds containing antimony. Both penicillin and streptomycin were found disappointing. *In vitro* studies by Wong and Cox (1948), Weiss (1950), and Gogolak and Weiss (1950) showed that aureomycin was more effective than penicillin against the causal organism of the disease, and Smadel and Jackson (1948) confirmed the activity of chloramphenicol. Hurst and others (1950), in experiments on the mouse and chick embryo, found aureomycin and terramycin equally effective in diminishing mortality and preventing inhibition of growth in infected animals. He found that, by these criteria, chloramphenicol was much less efficient, and combinations of aureomycin and penicillin gave results inferior to either drug alone. The carrier rate in surviving animals was high after aureomycin and terramycin, and reached nearly 100 per cent. after chloramphenicol. The experimental evidence would, therefore, appear to favour aureomycin and terramycin over chloramphenicol.

The clinical evidence is more conflicting. While Fletcher and others (1951), Prigot and others (1949), Wright and others (1948a, b), Greenblatt and others (1950), Schamberg and others (1951), and Canizares (1950) reported favourably on series of cases treated with aureomycin, and Norman (1951) and Benhamou and others (1949) on single cases, others (Robinson and others, 1950; Alergant, 1950; Olansky and Landman, 1950) did not achieve such consistently good results. Similarly there are varying opinions on the effect of chloramphenicol. Olansky and Landman (1950), Robinson and others (1950), Greenblatt and others (1950), and Canizares (1950) found this drug to be of little practical value, but Robinson (1951) and Rowe (1951) achieved satisfactory results by its use. In the two series so far treated with terramycin (Wright and others, 1951; Niedelman and others, 1951), the results were good.

While there appears, therefore, to be some use for each of these drugs in lymphogranuloma venereum, it is not yet possible to judge their relative merits. This is inevitable as long as criteria of cure and degrees of severity remain undefined, and different authorities employ different dosages and different modes of administration.

The usefulness of terramycin in the treatment of early lymphogranuloma venereum is confirmed by the present series. It is superior to sulphonamides reinforced by antimony.

We have not been able to compare terramycin directly with aureomycin and chloramphenicol. Until all three drugs have been tried on a large number of patients under standard conditions, it will not be possible to indicate finally which is the drug of choice.

However, there are other considerations apart from niceties of clinical response. Aureomycin is very expensive and chloramphenicol only slightly less so, whereas terramycin promises to be the cheapest of all three. The great majority of sufferers from this disease, which, though not fatal, is a distressing, crippling, and painful disorder, are out of reach of any of these drugs at the moment. The immediate problem is, therefore, to make a drug readily available to all who need it, which is cheap, effective, free of unpleasant and dangerous effects, and easily administered. Terramycin may eventually be regarded as coming nearest to a fulfilment of these criteria, and is perhaps, at the moment, the best available agent in the treatment of this preventable disease.

Summary

Nineteen cases of early lymphogranuloma venereum in young adult West African males were treated with terramycin 1 g. 6-hourly. In eighteen cases cure was achieved within an average of just over 7 days. One patient failed to respond.

The rate of cure is independent of co-existent latent syphilis.

Terramycin is significantly more effective than the standard treatment by sulphonamides and antimony previously in use.

The literature dealing with the treatment of lymphogranuloma venereum by means of the new antibiotics is briefly reviewed.

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